ORIGINAL ARTICLE

# Retrospective study of CMV retinitis in patients with AIDS

*M. Pauriah and E. L. C. Ong*

Department of Infection & Tropical Medicine, Newcastle University Medical School, Newcastle General Hospital, Newcastle-upon-Tyne NE4 6BE, UK

**Objective** To study the characteristics of clinical presentations and treatment outcome of patients with HIV infection who developed cytomegalovirus(CMV) retinitis.

**Methods** A retrospective study for the period 1986–97 at the regional Unit of Infectious Diseases, Newcastle General Hospital; a teaching hospital in the north-east of England. Twenty-seven patients with advanced HIV disease and clinically confirmed CMV retinitis were studied. The mean age was 40.8 years, standard deviation ±6.3 years. The male : female ratio was 25 : 2. Twenty-six of the patients were white Caucasians and one was of Afro-Caribbean origin.

**Results** The median time between the first AIDS-defining diagnosis and development of CMV retinitis was 1.5 years and the CD4+ cell count at the time of diagnosis of CMV retinitis was 7/mm$^3$. After 14 months of treatment. 80% of patients on mono antiretroviral therapy had impairment of sight (visual acuity 3/60) versus 30% for those on triple antiretroviral therapy. In the same period, the survival rate was 18 versus 70% for mono versus triple antiretroviral therapy, respectively.

**Conclusion** The outcome for patients with CMV retinitis was significantly better for those who were on triple than for those on mono antiretroviral therapy.

**Keywords** Cytomegalovirus retinitis, AIDS, Triple antiretroviral therapy, survival

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## INTRODUCTION

Cytomegalovirus (CMV) is a human herpes virus that contributes to morbidity and mortality among individuals with HIV infection. Overt CMV infection develops in 20% of HIV-infected individuals within 2 years once the CD4+ counts have fallen below 100/mm$^3$ [1]. Among homosexual individuals with AIDS, the rate of CMV seropositivity approaches 100% [2]. In autopsy studies, up to 90% of individuals with AIDS have histological evidence of CMV infection. CMV retinitis develops in 25 to 40% of individuals with AIDS and, if untreated causes progressive visual loss [3]. Although chorioretinitis is the most common presentation, CMV can also cause esophagitis, colitis, pneumonia and central nervous system disease.

The Department of Infection and Tropical Medicine in Newcastle-upon-Tyne is the tertiary referral centre for the care and treatment of individuals with HIV infection in the Northern region and in 1999 had 180 individuals under active follow-up. Patients with CMV retinitis were treated with intravenous ganciclovir as first choice and foscarnet as second choice. Induction therapy was administered for 2–3 weeks or until the retinitis stabilized. Ganciclovir 5 mg/kg twice a day or foscarnet 90 mg/kg were administered through an indwelling Nutricath (Vygon, Ecouen, France) catheter inserted subcutanously via the subclavian vein. Surgical placement of an intravitreal ganciclovir implant was introduced into clinical practice in 1997.

A retrospective study was undertaken to investigate the characteristics of clinical presentation and treatment outcome in individuals with HIV infection who subsequently developed CMV retinitis and to assess whether there had been any change in survival since the introduction of highly active antiretroviral therapy (HAART).

## METHODS

Twenty-seven patients with AIDS and confirmed CMV retinitis were identified from the hospital register records. The

Corresponding author and reprint requests: E. L. C. Ong, Department of Infection and Tropical Medicine, Newcastle University Medical School, Newcastle General Hospital, Newcastle-upon-Tyne NE4 6BE, UK
Tel: +44 (0) 191 273 8811
Fax: +44 (0) 191 219 5037
E-mail: e.l.c.ong@ncl.ac.uk

diagnosis of CMV retinitis was made clinically by characteristic fundoscopic appearances and positive CMV serology and by subsequent response to ganciclovir or foscarnet therapy. The hospital notes were examined and the following details extracted: age, sex, mode of acquisition of HIV infection, CD4+ count at presentation, antiretroviral therapy, date of diagnosis of CMV retinitis together with the CD4+ count at that time, treatment, side-effects of treatment and response. Information about the HIV viral load was not available in the majority of cases prior to October 1997.

## RESULTS

Of the 27 patients identified as having CMV retinitis, 20 (74%) had died and seven (26%) were still alive. Twenty-five (93%) were males; 26 (96%) were white Caucasians and one was an Afro-Caribbean. Their ages varied between 30 and 67, with two cases being aged 67 at the time of diagnosis of CMV retinitis.

Twenty-four (86%) acquired HIV infection through homosexual contact, one through heterosexual contact, another one through intravenous drug use and the exact route of infection of the remaining patient was unknown.

The CD4+ count at presentation of their HIV infection varied from less than 10 up to 530/mm$^3$ with a median of 100 cells/mm$^3$. Twenty (74%) patients had a count $<200$/mm$^3$.

Ten (37%) were on triple antiretroviral therapy combination, 14 (52%) were on mono antiretroviral therapy and the remaining three (11%) were on dual therapy. Patients treated with mono antiretroviral therapy were those in the early part of the study period who had died before the unit started the use of triple combination and those on dual therapy were those who could not tolerate the triple combination of drugs. Table 1 shows the details of each individual patient.

Twenty-two (81%) were initially treated with ganciclovir for retinitis, three (11%) with foscarnet and two had ganciclovir implants. Of those who were initially treated with ganciclovir, seven (32%) developed bone marrow suppression; for three patients (14%) it was severe enough to require a change to foscarnet. For those on foscarnet, two (66%) had to be changed to ganciclovir due to renal impairment caused by foscarnet.

### AIDS defining diagnosis and onset of CMV retinitis

The interval between the start of an AIDS-defining episode and the onset of CMV retinitis generally varied between 0 and 4 years, although it was 9 years for one patient as shown in Figure 1. This is a cumulative frequency curve displaying the total number of individuals developing CMV retinitis versus time. The median interval was 1.5 years and by 2.2. years 80% of the sample had developed this complication.

### CD4+ cell count at the time of diagnosis of CMV retinitis and progression of the disease

The CD4+ count of patients at the time of diagnosis of CMV retinitis varied from $<10$ up to 100/mm$^3$. Figure 2 shows the cumulative frequency curve of patients and their CD4+ counts. The median count was 7/mm$^3$ and 90% of patients with the disease had counts of $<51$/mm$^3$.

For the 14 patients on mono antiretroviral therapy, no impairment of sight in the affected eye developed during the first 5 months of treatment. For the eight who survived this period, five (63%) had impairment of sight in the affected eye (visual acuity 3/60) by 12 months. Only two were alive after 2.5 years and neither had evidence of active CMV retinitis. However, the outcome for those on triple therapy was different in that only three (30%) had visual acuity reduced to $\leqslant 3/60$ by the 14th month, compared with over 80% for those on mono antiretroviral therapy.

### Survival

Figure 3 shows the survival time in months after the diagnosis of CMV retinitis in patients on mono-antiretroviral therapy; 50% of the individuals who were on monotherapy had died in the 6 months following the diagnosis of CMV retinitis.

However, the results are quite different for patients on the triple combination of drugs. After 14 months of treatment, 70% were still alive compared with 18% on mono antiretroviral therapy. It should be noted that in fact only three patients on triple combination had died (one at 3 months, one at 9 months and the last at 29 months).

## DISCUSSION

This retrospective study showed that the median time between the first AIDS-defining event and developing CMV retinitis was 1.5 years and the median CD4+ count at the time of diagnosis was 7 cells/mm$^3$. Eighty per cent of patients on mono antiretroviral therapy after 14 months had impairment of sight compared with 30% of those who were being treated with the triple therapy. The survival rate was 18 versus 70%, respectively. The introduction of HAART has reduced the incidence of CMV infection in HIV-positive populations. The addition of protease inhibitors as part of the HAART has been documented to show beneficial effects in sustaining CD4+ counts particularly in the first 16 weeks of treatment. This corresponds with a prolonged period of inactive CMV retinitis [4] which we have similarly found in three of our patients in this study. Immunological reconstitution can occur after prolonged suppression of HIV activity suggesting that, for selected patients with healed CMV retinitis, temporary discontinuation of prophylaxis may not result in further retinal necrosis [5–7].

**Table 1** Patient details

| Patient | Ethnic origin, age, sex, mode of acquiring HIV infection | AIDS defining diagnosis (month/year) | Anti-retroviral treatment (side-effects) | Symptoms of CMV retinitis (months after AIDS defining diagnosis | CD4+ count (cells/mm$^3$)[a] | Anti-CMV treatment (side-effects) | Complications (months after anti-CMV treatment) | Follow-up months (alive/dead) |
|---|---|---|---|---|---|---|---|---|
| 1 | W/30/M/Ho | Esophageal candidiasis (12/93) | AZT (anaemia) DDC | Bitemporal visual field loss (18) | 30 | Ganc. (B.M. suppression) | None | 12 (dead) |
| 2 | W/37/M/Ho | *Pneumocystis carinii* pneumonia (8/97) | AZT (myopathy) DDI | Blurred vision (48) | 10 | Ganc. | None | 2 (dead) |
| 3 | W/67/M/Ho | Kaposi's sarcoma (?/88) | AZT-stopped (severe anaemia) DDI | Blurred vision (24) | 10 | Ganc. | None | 3 (dead) |
| 4 | W/32/M/Ho | *Pneumocystis carinii* pneumonia (9/90) | AZT-stopped (severe anaemia) DDI | Visual field defects (24) | 10 | Ganc. (pancytopenia) changed to Fosc. | None | 4 (dead) |
| 5 | W/40/M/Ho | *Pneumocystis carinii* pneumonia (9/94) | DDC | Visual field defects (13) | 10 | Ganc. | None | 4 (dead) |
| 6 | W/39/M/Ho | *Pneumocystis carinii* pneumonia (1/89) | AZT | Left visual field disturbance (48) | 10 | Fosc. (seizure) changed to Ganc. | None | 5 (dead) |
| 7 | W/33/M/Ho | *Pneumocystis carinii* pneumonia (5/93) | AZT, DDC (oesophageal ulceration) | Black spot in left eye (24) | 20 | Ganc. | None | 5 (dead) |
| 8 | W/32/M/Ho | Kaposi's sarcoma (11/91) | AZT | Blurred vision (30) | 40 | Foscarnet | VI (5) | 6 (dead) |
| 9 | W/34/M/Ho | *Pneumocystis carinii* pneumonia (?/88) | AZT (myopathy) DDI | Blurred vision in left eye (24) | 10 | Ganc. (B.M. suppression) | VI (8) | 9 (dead) |
| 10 | W/32/F/IVDA | Not available | AZT (non-compliant) | Visual field defect in left eye (?) | $<10$ | Ganc. (pancytopenia) | VI (9) | 10 (dead) |
| 11 | W/41/M/Ho | Esophageal candidiasis (3/90) | AZT (myopathy) DDI | Black spots (24) | 20 | Ganc. | Detached retina (7) | 11 (dead) |
| 12 | W/56/M/Ho | Kaposi's sarcoma (?/91) | AZT | Blurred vision (36) | 10 | Ganc. | VI (10) | 11 (dead) |
| 13 | W/29/M/Ho | *Pneumocystitis carinii* pneumonia (6/88) | AZT | Visual field loss (13) | $<10$ | Ganc. (?erythematous rash) | VI (12) | 15 (dead) |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 14 | W/45/M/Ho | *Pneumocystis carinii* pneumonia (1/89) | AZT (anaemia) DDI | Blurred vision (7) | 10 | Ganc. | None | 30 (dead) |
| 15 | W/39/M/Ho | *Pneumocystis carinii* pneumonia (11/92) | AZT | Blurred vision (1) | 10 | Ganc. | VI (36) | 42 (dead) |
| 16 | W/50/M/Ho | Esophageal candidiasis (10/94) | AZT 3TC D4T | Blurred vision (11) | 30 | Ganc. (neutropenia) | None | 15 (dead) |
| 17 | W/67/M/? | CMV retinitis (2/97) | DDI D4T SAQ. | Blurred vision (0) | 90 | Ganc. | None | 3 (dead) |
| 18 | W/67/M/? | *Pneumocystis carinii* pneumonia (1/90) | IND. DDC. NEV. | Film over left eye (30) | 20 | Ganc. | Detached retina (3) | 4 (alive) |
| 19 | W/31/M/Ho | *Pneumocystis carinii* pneumonia (3/97) | IND. DDC. NEV. | Blurred vision (2) | 10 | Ganc. | VI (3) | 9 (alive) |
| 20 | W/34/M/Ho | *Pneumocystis carinii* pneumonia (2/93) | AZT DDI IND. | Blurred vision (46) | 20 | Ganc. | None | 14 (alive) |
| 21 | W/46/M/Ho | Esophageal candidiasis (6/93) | 3TC NEV. IND. | Visual field defect (40) | 40 | Ganc. | None | 16 (alive) |
| 22 | W/42/M/Ho | Kaposi's sarcoma (?/87) | IND. D4T. 3TC | Blurred vision (108) | 100 | Ganc. (?photosensitivity) | Detached retina (6) | 16 (alive) |
| 23 | W/37/M/Ho | CMV retinitis (9/96) | SAQ. 3TC NEV. | Blurred vision (0) | 10 | Ganc. | None | 17 (alive) |
| 24 | W/41/M/Ho | *Pneumocystis carinii* pneumonia (12/95) | SAQ. (Renal failure DDC D4T | Visual field defect (9) | 10 | Ganc. | None | 19 (alive) |
| 25 | B/36/F/Hs | Disseminated TB (2/95) | SAQ. D4T (Peripheral neuropathy) IND. | Blurred vision (17) | 60 | Ganc. | VI (9) | 19 (dead) |
| 26 | W/50/M/Ho | *Pneumocystis carinii* pneumonia (11/93) | AZT (Anaemia) DDI DDC | Visual field defect (23) | 20 | Ganc. (line sepsis) | VI (11) | 21 (dead) |
| 27 | W/39/M/Ho | *Pneumocystis carinii* pneumonia (7/92) | IND. D4T | Visual field defect (17) | 50 | Ganc. (line sepsis) | VI (12) | 38 (dead) |

[a] At presentation of CMV retinitis; VI, Visually impaired.

Ho, Homosexual; Hs, Heterosexual; VDA, Intravenous drug abuse; W, White; B, Black; F, Female.

AZT, Azidothymidine; DDC, Zalcitabine; DDI, Didanosine; D4T, Stavudine; 3TC, Lamuvidine; NEV, Nevirapine; IND, Indinavir; SAQ, Saquinavir; Ganc, Ganciclovir; Fosc, Forscarnet; B.M., Bone marrow; TB, Tuberculosis.

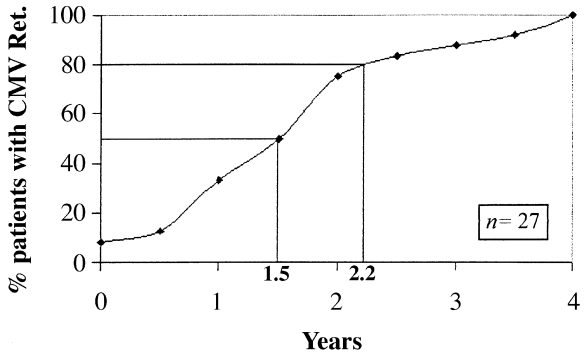


**Figure 1** Cumulative frequency curve showing total number of patients who developed CMV retinitis versus time.

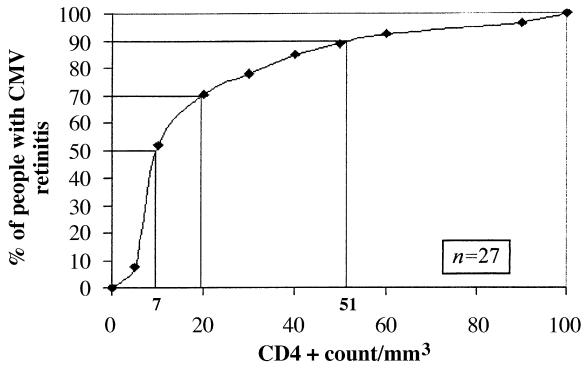


**Figure 2** Cumulative frequency curve of patients and CD4+ counts.

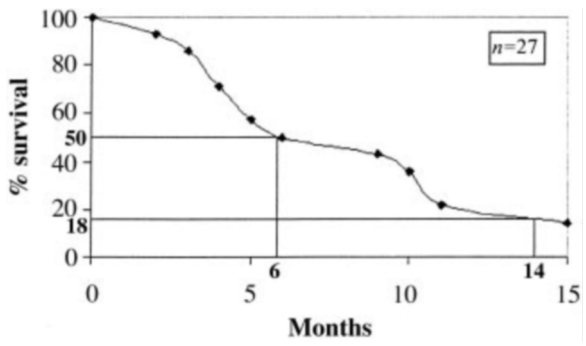


**Figure 3** Survival time of patients with CMV retinitis on mono antiretroviral therapy.

However, there have been reports of patients developing CMV retinitis while receiving HAART. CMV-specific T cells may have been exhausted in such patients and therefore no expansion of T cells to restore such immunity could be expected [8]. Alternatively, an improved CMV-specific immune response may have not penetrated the eye and this may explain why protease inhibitors prevented nonretinal CMV disease but not CMV retinitis in patients with advanced HIV disease [9].

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